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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 11/10/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/995,522

Applicant(s)

GELBER, COHAVA

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12, 14-32, 34-39, 51-56 and 65-80 is/are pending in the application.
- 4a) Of the above claim(s) 1-12, 14-17, 21-24, 30-32, 39, 43 and 51-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-20, 25-29 and 65-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's election with traverse of Group VII, claims 19-20 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that claims in Group VI and IX should be examined with the Group VII claims. The traversal is found persuasive and claims 18 and 25-29 will be examined with the Group VII claims. In addition newly submitted claims 65-80 will also be included in the examination. With respect to the other Groups in the restriction, the restriction stands because each group is patentable distinct as stated in the restriction requirement. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-12, 14-17, 21-24, 30-32, 34-39, 51-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

3. Claims 18-20, 25-29, 65-80 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:
a. The first line of the specification need to be updated to indicate that this application is a DIV of 09/374,367, now US Patent 6,376,654, issued 4/23/02.

Appropriate correction is required.

Claim Objections

5. Claims 18-20, 25-29, 65-69 are objected to because of the following informalities:
- a. Claims 18-20, 25-29, 65-69 are objected to for depending upon non elected claims. For the purpose of examination all claims depending on claim 1 and 5 will be examined with the limitations recited in claims 1 and 5.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 18-20, 25-29, 65-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 18-20, 25-29, 65-74 are indefinite for either depending on claim 1 and/or reciting "molecular weight of about 78 kDa to about 120 kDa or reciting "molecular weight of about 76 kDa to about 213 kDa" in claim 70 for the exact meaning of the phrases are not clear. The molecular weights are determined by SDS PAGE under reducing conditions but it is unclear what the recited range encompasses. Does about 78 kDa to about 120 kDa encompass 50 kDa, 60 kDa, 150 kDa, 200 kDa?

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Additionally it is not clear what range is encompassed by about 76 kDa to about 213 kDa. Does this phrase encompass 50 kDa, 60 kDa, 230 kDa, 250 kDa? In addition, it is also unclear how a single polypeptide can have a molecular weight of "about 78 kDa to about 120 kDa" or a single, glycosylated polypeptide can have a molecular weight of "about 76 kDa to about 213 kDa".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 19-20, 25-29, 75-80 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of MA69 having the accession No. PTA-450 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape,

antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993), IDS #3]. Therefore, it would require undue experimentation to reproduce the claimed antibody species MA69. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicants referral to the deposit of the hybridoma producing the MA69 antibody on page 27, lines 1-3 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met. In addition, the deposit was made after the effective filing date of the application and as such a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the cell line has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when

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deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

10. Claims 18-20, 25-29, 65-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an antigen on the surface of myeloma cells or ovarian cells wherein the antigen has a molecular weight of about 78 kDa to about 120 kDa and is not on blood mononuclear cells, B cells, and myelogenic leukemia cells and is glycosylated or on the surface of ovarian cancer cells which is a single glycosylated polypeptide of about 76 kDa to about 213 kDa, does not reasonably provide enablement for a method of inhibiting the growth of myeloma or ovarian tumor cells with an antibody that binds an antigen characterized in that the antigen has a molecular weight of about 78 kDa to about 120 kDa and is not on blood mononuclear cells, B cells, and myelogenic leukemia cells and is glycosylated or on the surface of ovarian cancer cells which is a single glycosylated polypeptide of about 76 kDa to about 213 kDa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in

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the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to method of inhibiting the growth of or killing of myeloma or ovarian cancer cells with antibodies that are labeled or unlabeled that bind to any antigen on the surface of any human myeloma cell wherein the antigen has a molecular weight of about 78 kDa to about 120 kDa and is not on blood mononuclear cells, B cells, and myelogenic leukemia cells and is glycosylated. Further, the claims broadly encompass an methods with an antibody that recognizes an antigen on the surface of ovarian cancer cells which is a single glycosylated polypeptide of about 76 kDa to about 213 kDa and an antibody that binds to the same antigenic determinant as the monoclonal antibody PTA-450.

The specification discloses that the antigen to which the claimed monoclonal antibody binds is glycosylated, however, no direct evidence is presented that the antigen is glycosylated. The specification teaches on page 15, lines 13-18 that the monoclonal antibody "MA69 recognizes one or more glycoproteins ranging in size from 76 to 213 kDa. These results imply that MA69 reacts with 2 distinct molecules expressed on MM and ovarian cancer". The specification does not teach that either a labeled or unlabeled antibody can inhibit growth or kill the cells

Claim 5 (wherein the limitations of claim 5 are being examined in the instant claims) claim antibodies which are capable of binding to the same antigenic determinant

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as monoclonal antibody having ATCC accession No. PTA-450, however, the antigenic determinant or epitope is not disclosed in the specification. It was not disclosed if the epitope is a continuous linear epitope of amino acids or a discontinuous conformational epitope of amino acids or if the epitope contains carbohydrate moieties.

As taught by Cruse et al (Illustrated Dictionary of Immunology, CRC Press , page 22, 1995, IDS #3) an antigenic determinant is defined as “the site on an antigen molecule that is termed an epitope and interacts with the specific antigen-binding site in the variable region of the antibody molecule”. Claims 19, 20, 25-29 are directed to methods using antibodies which are capable of binding to the same antigenic determinant as the monoclonal antibody produced by hybridoma cell line PTA-450, however, the specification does not disclose the epitope with which the antibody produced by hybridoma PTA-450 binds. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999), IDS #3) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. “In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects”. “Even when the residues making contacts with ligands are known with

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certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

The specification does not disclose if the epitope is a carbohydrate moiety. Recognition of carbohydrate moieties bound by antibodies is a complex and unpredictable task. Unlike linear amino acid epitopes, which can be readily synthesized in vitro and against which other antibodies can be readily made, carbohydrate epitopes are more complex and difficult to synthesize. Knight (BioTechnology Vol 7 No 1, Jan 1989, IDS#3) likens this task to "wrestling with a cloud". She states that "prediction and control of the expression of oligosaccharide remains elusive and threatens to remain so from some time" and the challenge is "a daunting one". Knight goes on to explain that "the structure of carbohydrates is much more complex than that of proteins. Dwek likens the task of sequencing a carbohydrate to "simultaneously sequencing 40 or 50 proteins". Because carbohydrate structures are a branching series of linked rings, they can combine in many more ways than linear peptide chains. For comparison, consider that while three amino acids can combine in only six ways, three carbohydrate monomers can form over 1,000 different trisaccharide structures" (see page 39, first column, third and fourth full paragraphs). One skilled in the art would reasonably conclude that, even if one had known that the epitope

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comprised carbohydrate moieties, the synthesis of potential carbohydrate moieties would require undue experimentation.

Even if one skilled in the art were able to identify a region of a glycosylated protein that bound a particular antibody, Knight teaches the unpredictability of knowing the exact structure found in that glycoprotein. Knight states that “on top of this amazing diversity, nature adds what glycobiologists call “micro heterogeneity” in the form of discrete subsets -glycoforms- of a glycoprotein. These may have difference physical and biochemical properties.” One skilled in the art would reasonably conclude that these different physical and biochemical properties encompass expression of different epitopes. Knight summarize that “the “demographics” of its glycoform population determine the composite activity of a glycosylated compound. According to Rademacher, Parekh and Dwek, “Any given glycoprotein that consists of different glycoforms will... have a composite activity, reflecting a weighted average of the activity and incidence of each glycoform” (page 39, third column, second full paragraph). In summary, antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. The nature of the epitope was unknown at the time of filing. While multiple antibodies can be readily made to linear peptide sequences, the same is not true of antibodies that recognize non-linear conformational determinants such as carbohydrate epitopes.

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between in vitro

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data and *in vivo* for inhibiting tumor growth. The *in vitro* experimental data presented is clearly not drawn to subjects with tumor cells and only demonstrates a method of detecting the antigen (see Examples 2-5). The invitro data only shows the detection of an antigen in the cells and no inhibition of growth or killing of the tumor cells in vitro or in vivo with an antibody that is either labeled or unlabeled. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been

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in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, the antibodies would be used for treatment of cancer.

Further, One cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para).

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation.

11. Claims 18-20, 25-29, 65-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

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to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of inhibiting or killing myeloma or ovarian cancer cells with an antibody or binding fragment thereof which binds to an antigen on the surface of human myeloma cells wherein the antigen is characterized in that it is a single polypeptide with a molecular weight of about 78 kDa to about 120 kDa and is absent from human peripheral blood mononuclear cells, human B cells, human B cell myelogenic leukemia cells and is glycosylated and an antibody which recognizes an antigen present on the surface of ovarian cancer cells which is glycosylated and has a molecular weight of about 76 kDa to about 213 kDa. Further the claims are broadly drawn to methods using antibodies which bind to a cell surface glycoprotein antigen of human myeloma tumor cells such that the antibodies are capable of binding to the same antigenic determinant as the antibody produced by the hybridoma PTA-450. The claims read on a broad group of antibodies for the claimed method, however, the specification only discloses one antibody with the claimed characteristics, that being the MA69 antibody produced by the hybridoma cell line PTA-450. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 18, 65, 70, are rejected under 35 U.S.C. 102(b) as being anticipated by Lloyd et al (Int. J. Cancer 71:842-850, 1997, IDS paper #3).

The claims are enabled for a method of detection of myeloma or ovarian cancer cells with a monoclonal antibody which specifically binds to an antigen on the surface of human myeloma cell said antigen characterized by being a single polypeptide with a molecular weight of about 78 kDa to about 120 kDa and is absent from human peripheral blood mononuclear cells, human B cells, and human B cell myelogenic leukemia cells and is glycosylated. Further the antibody recognizes an antigen on the surface of ovarian cancer cells an the antigen is a single glycosylated polypeptide with a molecular weight of about 76 kDa to about 213 kDa.

Lloyd et al teach a method of detection of ovarian cancer cells with a monoclonal antibody which specifically binds to the antigen CA 125 which is a glycosylated polypeptide of molecular weight of 50-200 kDa on the surface of ovarian cancer cells (see page 842).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 18-20, 25-26, 65-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lloyd et al (Int J. Cancer 71:842-850, 1997, IDS paper #3) as applied to claim above, and further in view of Harlow et al (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, pp 319-329, 626-631, 1988, IDS #3).

Claims 18, 65, 70 have been described supra for their enabled scope. Claims 19-20, 25-26, 65-74 recite wherein the antibody binding fragment is a F(ab')₂ and the antibody is radiolabeled.

Lloyd et al has been described supra. Lloyd et al does not teach a F(ab')₂ antigen binding fragment or radiolabeling of the antibody. These deficiencies are made up in the teachings of Harlow et al.

Harlow et al teach proteolytic fragments of antibodies (see pages 626-631) and labeling of antibodies with ¹²⁵I (see pages 319-329).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody described by Lloyd and radiolabel it and produce a F(ab')₂ antigen binding fragment as taught by Harlow et al for a method of detecting the antigen in cells.

One of ordinary skill in the art would have been motivated to have used the antibody described by Lloyd and radiolabel it and produce a F(ab')₂ antigen binding

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fragment as taught by Harlow et al for a method of detecting the antigen in cells because Harlow et al teach "The use of an intact antibody molecule in some immunochemical techniques introduces certain problems....These problems and others like them can be overcome by using fragments of the antibody." (See page 626) and "a wide range of immunological techniques depend on the use of labeled antibodies." (See page 321). In addition, one of ordinary skill in the art would have been motivated to have used the antibody described by Lloyd and radiolabel it and produce a F(ab')₂ antigen binding fragment as taught by Harlow et al for a method of detecting the antigen in cells because Lloyd et al teach "Mab OC125, the prototype antibody detecting CA 125, has also been studied as an imaging and therapeutic agent in ovarian cancer" (see page 842). Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in using the antibody described by Lloyd and radiolabel it and produce a F(ab')₂ antigen binding fragment as taught by Harlow et al for a method of detecting the antigen in cells because Harlow et al teach "Iodination of antibodies and other proteins is straightforward and effective method of labeling." (See page 324) and "determining the correct conditions for pepsin treatment is relatively easy." (See page 630).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

16. No Claims are allowed.

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17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D
PRIMARY EXAMINER